REMARKS/ARGUMENTS

Upon entry of this amendment, claims 38 and 44-46 will be pending in the application. Claims 1-37 and 39-43 have been canceled. Claims 38 and 44-46 have been amended to provide broader claim coverage of the present invention and to overcome the rejection for alleged new matter. No new matter has been introduced by way of this amendment.

Applicants note with appreciation the withdrawal of the objections to the specification and drawings and of several rejections to the claims.

Preliminarily, Applicants respectfully submit that the finality of the Office action mailed June 4, 2003 is improper. In accordance with 35 U.S.C. § 132, a second or subsequent action on the merits cannot be made final where the Office action introduces a new ground of rejection not necessitated by applicant's amendment or based on newly cited art in response to an amendment which should reasonably have been expected by the examiner. The present Office action cites U.S. Patent No. 6,054,132 as basis for a 35 U.S.C. § 102(e) rejection for alleged obviousness of claims 44 and 46. Applicants respectfully submit this is a new ground of rejection which is not necessitated by Applicants' amendment. Accordingly, Applicants respectfully request withdrawal of the finality of the Office action.

I. Claims 38 and 44 remain provisionally rejected for alleged double patenting.

The provisional rejection of claim 44 for alleged obviousness-type double patenting over claims 63-66, 72-75, 84-86, and 93-101 of the copending application, Serial No. 09/360,934, has been maintained. Likewise, claim 38 is provisionally rejected for alleged

obviousness-type double patenting over claims 63-66, 75, 84-86, 93, 94, and 97-101 of the copending application, Serial No. 09/360,934. Applicants disagree for the reasons of record. Nonetheless, without conceding the obviousness of claims 38 and 44 in view of the cited claims of the copending application, Applicants submit that a terminal disclaimer over Application Serial No. 09/360,934 will be filed upon receipt of an indication of allowability of the cited claims in that case and of claims 38 and 44 in the present case.

II. Claims 38 and 44-46 satisfy the second paragraph of 35 U.S.C. § 112.

Claims 38 and 44-46 are rejected under 35 U.S.C. § 112, second paragraph for alleged indefiniteness in the recitation of the term "substantially." Applicants disagree with the rejection.

The term "substantially" often is used in conjunction with another term to describe a particular characteristic of a claimed invention. MPEP §2173.05 (b). Definiteness will be found for use of the term "substantially" where there are general guidelines in the specification (*In re Mattison*, 509 F.2d 563, 184 U.S.P.Q. 484 (C.C.P.A. 1975)) or where one of ordinary skill in the art would understand the meaning of the term (*Andrew Corp. v. Gabriel Electronics*, 847 F.2d 819, 6 U.S.P.Q. 2d 2010 (Fed. Cir. 1988)). Both of these instances occurs in the present case. As previously asserted, one of ordinary skill in the art would understand the use of the term "substantially" in the present context to mean that the polypeptide or fragment being described does not exhibit statistically significant cytotoxic effects. Indeed, Applicants have provided a Declaration of Dr. Del Giudice to substantiate this assertion.

Moreover, the specification provides very clear guidance as to the meaning of the term "substantially" as used therein. For example, at page 16, lines 19-29, the terms "purified" and "isolated" are defined as "substantial absence of other biological macromolecules of the same type" – *i.e.*, "at least 75% by weight, more preferably at least 85% by weight, more preferably still at least 95% by weight, and most preferably at least 98% by weight, of biological macromolecules of the same type." In other words, substantially pure means at least 75% pure. Similarly, "substantially no toxicity or a substantially reduced toxicity" means at least a 75% reduction in toxicity.

The Examiner additionally asserts that it is unclear to what kind of toxicity the phrase refers. Applicants disagree. Applicants use the terms "toxin" and "cytotoxin" and derivatives thereof interchangeably in the specification. Indeed, "cytotoxin" and "toxin" are defined synonymously in the specification at page 5, line 31 to page 6, line 11. The 140 kDa protein set forth in Fig. 2 is the precursor protein to the 100 kDa polypeptide having cytotoxic activity – *i.e.*, vacuolating activity (Specification at page 5, lines 35-39 and page 46, lines 7-29, for example).

In view of the guidance provided by the specification and the knowledge of one of ordinary skill in the art, Applicants maintain that the phrase "substantially no toxicity, or a substantially reduced toxicity" satisfies the requirements of section 112. Accordingly, Applicants respectfully request reconsideration and withdrawal of the rejection.

III. Claim 38 and 44-46 are enabled in accordance with the first paragraph of 35 U.S.C. § 112.

Claims 38 and 44-46 are rejected under 35 U.S.C. § 112, first paragraph for alleged lack of enablement of a cytotoxin polypeptide having "substantially no toxicity" or "substantially reduced toxicity" that is "immunologically identifiable by an antibody that reacts specifically with *Helicobacter pylori* cytotoxin." Applicants traverse the rejection.

The test of enablement is whether the disclosure, when filed, contained sufficient information regarding the subject matter of the claims as to enable one skilled in the pertinent art to make and use the claimed invention without undue experimentation. *In re Angstadt*, 537 F.2d 498, 504, 190 U.S.P.Q. 214, 219 (CCPA 1976); MPEP § 2164.01.

One skilled in the art of immunology would have been able to make and use the claimed immunogenic compositions at the filing of the priority application. As explained in the specification, the *H. pylori* cytotoxin causes formation of vacuoles in eukaryotic cells (Specification at page 5, lines 35-39 and page 46, lines 7-29, for example). The polypeptide of the claimed immunogenic compositions, however, exhibits substantially no toxicity, or substantially reduced toxicity. For example, the polypeptide of the claimed compositions may exhibit substantially no toxicity or substantially reduced toxicity by virtue of being recombinantly produced. Indeed, the recombinantly produced 95 kDa polypeptide taught by Manetti *et al.* (*Infection and Immunity*, 63(11):4476-4480 (1995) (already of record)), though immunogenic, lacks toxicity. *See also*, Ghiara *et al.*, *Infection and Immunity*, 65(12) 4996-5002 (1997) (already of record). The polypeptide of the claimed compositions may be a genetically or chemically detoxified form of the cytotoxin, or a fragment of the native cytotoxin, having no toxicity.

It is axiomatic that the patent applicant need not teach that which is known in the art. *Hybritech, Inc. v. Monoclonal Antibodies, Inc.*, 802 F.2d 1367, 1379-80, 231 U.S.P.Q. 81, 90 (Fed. Cir. 1986); MPEP § 2163 II.A.2. Methods of generating detoxified toxins were known in the art at the time of filing. Indeed, Dr. Del Giudice has attested that methods of chemical and genetic inactivation of toxins were known to those of skill in the art in March 1992. Dr. Del Giudice further has declared that it would have been routine for the skilled artisan to generate cytotoxin fragments. Moreover, Dr. Del Giudice has confirmed that it would have been routine to determine the polypeptides that exhibit substantially no toxicity or substantially reduced toxicity. Toxicity could be measured, for example, in *in vitro* vacuolation assays and in animal models of *H. pylori* infection routinely used in the art at the time of the present invention.

It has been asserted that the present specification teaches to the contrary in stating that examples of proteins within the scope of the invention include polypeptides with minor amino acid variations that do not substantially affect the functional aspects or biological activity. Applicants disagree. Nowhere in the specification is the definition of cytotoxin polypeptides within the scope of the invention limited to those that exhibit toxicity. In fact, the specification clearly contemplates immunogenic compositions comprising cytotoxin polypeptides that are capable of eliciting *protection* against *H. pylori* (Specification at page 15, lines 14-17; page 38, line 31 to page 41, line 17).

Turning to the immunogenicity element of the claims, the specification states that "[t]he *H. pylori* proteins [of the invention] may be used for producing antibodies, either monoclonal or polyclonal, *specific to* the proteins. The methods for producing these antibodies are known in the art." Specification at page 15, lines 18-21. Indeed, Dr. Del

Giudice affirms that it would have been routine in the art at the time of filing the present application to determine the immunogenicity of the polypeptides of the claimed compositions. Additionally, the specification teaches by way of example how to make and use a polypeptide that is immunologically identifiable by antibodies that react with the *H. pylori* cytotoxin (Specification at page 45, line 25 to page 46, line 6 (describing a fusion protein comprising the amino acids encoded by nucleotides 116-413 of the nucleotide sequence of SEQ ID NO:2 that generated rabbit antibodies that recognized the 100kDa *H. pylori* protein associated with vacuolation – *i.e.*, was immunologically identifiable by rabbit antibodies that recognize the toxic form of *H. pylori* cytotoxin)). That the methods used to produce a polypeptide exhibiting substantially no toxicity or substantially reduced toxicity may reduce the effective immunogenicity relative to the fully toxic polypeptide is irrelevant to the present enablement analysis so long as some level of immunogenicity remains.

As the skilled artisan would have been able to make and use the claimed immunogenic compositions at the time of filing the priority application using only the application as a guide combined with the knowledge of one skilled in the art, claims 38 and 44-46 satisfy the enablement requirement of the first paragraph of section 112. Accordingly, Applicants request reconsideration and withdrawal of the rejection.

IV. Amended claims 38 and 44-46 are adequately described in accordance with the first paragraph of 35 U.S.C. § 112.

Claims 38 and 44-46 are rejected under 35 U.S.C. § 112, first paragraph for alleged new matter. Applicants have amended claims 38, 44, and 46 to overcome the rejection and traverse with respect to claim 45.

Cytotoxin proteins of the invention that "exhibit substantially no toxicity or substantially reduced toxicity" are supported, for example, by claim 8 as originally filed. Support for such cytotoxin proteins that also are "immunologically identifiable by an antibody that reacts specifically with *Helicobacter pylori* cytotoxin" is found throughout the specification as filed. The specification states that "[t]he *H. pylori* proteins [of the invention] may be used for producing antibodies, either monoclonal or polyclonal, *specific to* the proteins." Specification at page 15, lines 18-20. Additionally, the specification discloses the preparation of antisera against the *Helicobacter pylori* cytotoxin and the use of the antisera to specifically detect polypeptides immunologically identifiable with the *H. pylori* cytotoxin. *See, e.g.,* Specification at page 45, line 26 to page 46, line 6.

As the claimed compositions are fully supported by the application as filed, Applicants respectfully request withdrawal of the rejection.

V. Claims 44 and 46 are patentable over the Cover references.

Claims 44 and 46 are rejected under 35 U.S.C. § 102 as allegedly being anticipated by U.S. Patent No. 6,054,132 to Cover *et al.* ("the '132 patent") or by Cover *et al.* (*J. Biol. Chem.*, 267:10570-10575 (1992)) ("the Cover article"). Applicants traverse the rejections.

Preliminarily, Applicants note that the Cover article is not prior art under 35 U.S.C. § 102(e).

To anticipate a claim, a prior art reference must teach, either expressly or inherently, each and every element of the claim. *See Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631 (Fed. Cir. 1987).

The rejected claims recite immunogenic compositions of a polypeptide having at least a portion of the amino acid sequence of SEQ ID NO:3 having the properties of being immunologically identifiable by antibodies that react specifically with *H. pylori* cytotoxin and exhibiting substantially no toxicity or substantially reduced contribution to toxicity.

In sharp contrast, the '132 patent discloses the purification of a vacuolating toxin of *H. pylori* having a molecular weight of 87 kDa wherein the purification scheme resulted in a greater than 5000-fold increase in specific activity of the toxin measured as a function of cell vacuolating activity ('132 patent, Table 1). In other words, the '132 patent does not teach, either expressly or inherently, the claimed immunogenic compositions comprising a polypeptide possessing substantially no toxicity or substantially reduced contribution to toxicity.

Similarly, the Cover article describes purification of the vacuolating toxin of *H. pylori* from *H. pylori* broth culture supernatant resulting in a 5000-fold increase in specific activity, measured again as a function of cell vacuolation. Thus, the Cover article also does not teach, either expressly or inherently, the claimed immunogenic compositions comprising a polypeptide possessing substantially no toxicity or substantially reduced contribution to toxicity.

Applicants accordingly request reconsideration and withdrawal of the rejections.

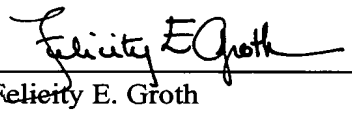
CONCLUSION

In view of the foregoing, Applicants believe all claims now pending in this application are in condition for allowance. The issuance of a formal Notice of Allowance at an early date is respectfully requested.

If the Examiner believes a telephone conference would expedite prosecution of this application, the undersigned may be contacted at 215-557-5908.

Respectfully submitted,

Date: November 26, 2003



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